UNIVERSIDAD AUTONOMA DE MADRID

TESIS DOCTORAL

ENSAYO CLÍNICO ALEATORIZADO COMPARATIVO ENTRE LA TERAPIA SECUENCIAL Y LA CONCOMITANTE PARA LA ERRADICACIÓN DE *Helicobacter pylori* EN LA PRÁCTICA CLÍNICA.

DOCTORAL THESIS

RANDOMIZED CLINICAL TRIAL COMPARING SEQUENTIAL AND CONCOMITANT THERAPIES FOR *Helicobacter pylori* ERADICATION IN ROUTINE CLINICAL PRACTICE

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RESUMEN

Objetivos:

Ningún ensayo ha comparado las terapias cuadruple sin bismuto "secuencial" y "concomitante" en áreas con frecuencias de resistencia a claritromicina en aumento. El objetivo del presente estudio es comparar la eficacia y seguridad de ambas terapias en el tratamiento de la infección por *H. pylori*.

Diseño:

Ensayo clínico prospectivo aleatorizado en 11 hospitales españoles. Pacientes que no habían recibido tratamiento erradicador previo con dispepsia funcional o no investigada o enfermedad por úlcera péptica, fueron aleatorizados (1:1) al tratamiento secuencial {Omeprazol (20 mg/12h) y amoxicilina (1 g/12h) durante 5 días seguidos de 5 días de omeprazol (20 mg/12h), claritromicina (500 mg/12h) y metronidazol (500 mg/12h)} o al concomitante (misma medicación tomada de forma concomitante durante 10 días). La erradicación se confirmo con la prueba del aliento de la urea-C^{13} o histología 4 semanas tras el tratamiento. Los efectos adversos (EA) y cumplimiento se evaluaron con cuestionarios y recuento de la medicación residual.

Resultados:

Se aleatorizaron 338 pacientes. La edad media fue de 47 años, el 60% eran mujeres, el 22% fumadores y el 20% sufría de úlcera péptica. Las tasas de erradicación de las terapias concomitante y secuencial fueron respectivamente 87% y 81% por intención de tratar (p = 0,15) , y 91% y 86% (p = 0.131) por protocolo. Los cumplimientos fueron respectivamente 83% y 82%. Se notificaron EA causados por el tratamiento en el 59% de los pacientes (sin diferencias entre ambos tratamientos). La mayoría (60%) de los EA fueron

leves con una duración media de 6,1 días, causando la retirada del tratamiento en 12 pacientes. En el análisis multivariante, el tratamiento concomitante mostro una razón probabilidades de 1,5 hacia mejores tasa de erradicación con un intervalo de confianza limite en la significación (I.C. 95% = 0,9-2,8)

Conclusión:

La terapia cuádruple sin bismuto "concomitante" conllevo una ventaja (5%) no estadísticamente significativa sobre la terapia "secuencial", llegando a valores más cercanos al 90% de erradicación. Ambos tratamientos mostraron un perfil de seguridad aceptable.

ClinicalTrials.gov: NCT01273441

SUMMARY

Objectives:

No trial has compared non-bismuth quadruple "sequential" and "concomitant" regimens in settings with increasing clarithromycin rates. The study aims to compare the effectiveness and safety of these therapies for *H. pylori* treatment.

Design:

Prospective randomized clinical trial in 11 Spanish hospitals. Patients naïve to eradication therapy with non-investigated/functional dyspepsia or peptic ulcer disease were randomized (1:1) to sequential {omeprazole (20mg/12h) and amoxicillin (1g/12h) for 5 days, followed by 5 days of omeprazole (20mg/12h), clarithromycin (500mg/12h) and metronidazole (500mg/12h)} or concomitant treatment (same drugs taken concomitantly for 10 days). Eradication was confirmed with ^{13}C-urea breath test or histology 4 weeks after treatment. Adverse events (AEs) and compliance were evaluated with questionnaires and residual medication count.

Results:

338 consecutive patients were randomized. Mean age was 47 years, 60% were females, 22% smokers, and 20% had peptic ulcer. Concomitant and sequential eradication rates were, respectively, 87% vs. 81% by intention-to-treat (p=0.15) and 91% vs. 86% (p=0.131) per-protocol. Respective compliances were 83% vs. 82%. Treatment-emergent AEs were reported in 59% of patients (no differences found between treatments). AEs were mostly mild (60%), and average length was 6.1 days, causing discontinuation only in 12 patients. In the multivariate analysis, "concomitant" treatment showed an odds ratio of 1.5

towards better eradication rate in a borderline significance confidence interval (95%CI=0.9-2.8).

Conclusion:

Non-bismuth quadruple “concomitant” therapy led to a non-statistically significant advantage (5%) over “sequential” therapy, coming closer to 90% cure rates. Both therapies showed an acceptable safety profile. ClincialTrials.gov: NCT01273441.

INTRODUCTION

Helicobacter pylori (*H. pylori*) causes the most common chronic bacterial infection affecting over 50% of the world's population (more than 80% in developing countries)[1]. Although most *H. pylori*-positive individuals will remain asymptomatic through life, its presence causes chronic gastritis in 100% of infected patients and is the major cause of relevant diseases such as atrophic gastritis, peptic ulcer disease and gastric cancer[2]. *H. pylori* eradication prevents peptic ulcer recurrence and its complications[3]. The W.H.O's International Agency for Research on Cancer classified *H. pylori* as a group 1 (definite) carcinogen[4]. Eradication in patients with peptic ulcer or even functional or non-investigated dyspepsia is a cost effective approach[2].

Most Consensus Conferences and Clinical Guidelines recommend the prescription of a triple therapy including a proton pump inhibitor (PPI) and clarithromycin with either amoxicillin or metronidazole, as first line treatment[2, 5-9]. However, with the increasing development of *H. pylori* resistance to antibiotics in most countries[10], the eradication rates of *H. pylori* with triple therapies are decreasing to unacceptable levels (≤80%)[11, 12]. Due to the low efficacy achieved with these treatments, they have been deemed as unethical comparators in clinical trials[13, 14]. As antimicrobial resistance becomes more prevalent worldwide, treatment failure rates are likely to continue increasing, suggesting that new regimens for *H. pylori* eradication must be sought.

All this has led the medical and scientific community to pursuit strategies that will improve treatment efficacy. One of the last therapeutic innovations in the field of *H. pylori* eradication is sequential treatment, introduced in Italy by Zullo et al[15], which consisted in an induction phase of 5 days with amoxicillin

and a PPI, immediately followed by 5 days of triple therapy (metronidazole, clarithromycin and PPI). Some authors argue that the beneficial effect of sequential treatment is only due to the use of an additional antibiotic[16]. Thus it has been suggested that all drugs could be given concomitantly, reducing the complexity of the regimen[17].

However, sequential and concomitant regimens have only been compared one to one and under similar conditions in 3 studies[18-20]. The three studies were performed in settings from Asia with low clarithromycin resistance, Other studies have compared sequential and concomitant regimens but with different duration of treatment arms[21, 22]. No study comparing both regimens with the same duration of treatment has been conducted in Europe, where clarithromycin resistance rates have increased dramatically over the years[10].

A meta-analytical approach could have been pursued; this approach has been widely used in the evaluation of *H. pylori* eradication; however, traditional meta-analyses of direct comparisons have suffered from heterogeneity and inconsistency. The lack of homogenous designs, dosages, and treatment lengths of clinical trials forces researchers to combine highly heterogeneous data in order to obtain a statistically significant odds ratio. This in turn has caused inconsistency of meta-analytical results depending on subjective selection criteria. Moreover, the flexibility of selection criteria in order to increase statistical significance has generally been performed accepting heterogeneous designs but it has been unable to incorporate valuable data from trials evaluating the studied regimens against other comparators.

AIM

Given the differences and limitations of previous studies, the aim of the present randomized controlled trial was to compare the effectiveness, safety and compliance of non-bismuth quadruple sequential and concomitant therapies for *H. pylori* treatment mimicking routine clinical practice in a large sample of patients and to meta-analyse its results with previously published data in a combined direct and indirect comparison.

METHODS

Design summary and Ethical Issues

The study was designed as a multicenter parallel, controlled, randomized, phase IV, non-commercial, independent trial. The study was co-funded by a Spanish Health Ministry Grant on Independent Drug Research (Grant number TRA-047) and by the organizing research team's own funds. Eleven Spanish hospitals from different regions participated. Patients were included from December 2010 to May 2012.

The study received approval and was audited by the Ethics Committees of all participant hospitals, and by the Drugs National Authority. This study was conducted in accordance with the principles of the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations.

Written informed consent was obtained from all patients before enrolment.

Study population

Inclusion criteria: Participants with non-investigated/functional dyspepsia or gastroduodenal ulcer with indication of *H. pylori* eradication treatment by routine clinical practice; ability and willingness to participate in the study and to sign and give informed consent; confirmed *H. pylori* infection by at least one of the following methods: ^{13}C-Urea breath test, histology, rapid urease test or bacterial culture.

Exclusion criteria: Age below 18 years; advanced chronic disease that would not allow the patient to complete follow up or attend to visits; allergy to any of the study drugs; previous gastric surgery; pregnancy or breastfeeding (female participants with childbearing potential were required to use medically accepted contraception for the duration of the study); alcohol or drug abuse; previous *H. pylori* eradication treatment; and taking antibiotics or bismuth salts four weeks prior to inclusion.

Intervention

Sequential treatment group: Induction phase of 5 days under dual therapy (omeprazole 20 mg/12h, and amoxicillin 1 g/12h) immediately followed by a treatment phase of 5 days under triple therapy (omeprazole 20 mg/12h, clarithromycin 500 mg/12h and metronidazole 500 mg/12h).

Concomitant treatment group: 10 days under quadruple therapy (omeprazole 20 mg/12h, amoxicillin 1 g/12h, clarithromycin 500 mg/12h and metronidazole 500 mg/12h).

All drugs used in both therapies were of generic branding.

Trial bias minimization

Randomization: Patients were allocated to one of the treatment arms (sequential treatment or concomitant treatment) using a 1:1 computerized random number table. Allocation was stratified by hospital and presence or not of ulcer disease and blocked in tandems of 6.

Allocation concealment: Allocation was concealed (opaque sealed envelopes) and the coordinators and the investigators in the centers did not know the details of the allocation sequence.

Blinding: This trial was unblinded; the number of drugs to be taken and the dosing are different among arms and the principal outcome is *H. pylori* eradication, which is not influenced by the unblinded design of the protocol. Urea breath test personnel, endoscopists and pathologists were blind to treatment given.

Treatment was clearly explained to all patients. Study drugs were handed to the patient in a registered box that included all the required pills and a day by day intake scheme and diagram. Drugs were self-administered orally at home after meals. All non-study medication took by the patient during the study was recorded.

Trial outcomes

Primary Outcome: Confirmed *H. pylori* eradication by intention to treat a minimum of 4 weeks after ending treatment using ^{13}C-urea breath test or histology. Prior to testing, patients had to withdraw PPI treatment (15 days) and any antibiotic treatment (1 month).

Secondary Outcomes: Compliance cut-off point was set in taking at least 90% of each study drug. Per protocol analysis of *H. pylori* eradication; compliance to treatment regimen (patient interrogation and residual drug count, checked by the clinical trial monitor); and treatment-emergent adverse event/adverse reaction via open answer general question, and specific

questionnaire of commonly described adverse events to treatment, as well as a biochemical and hematological blood analysis. Any discomfort, even if mild, referred by the patients and evaluated by their doctors as related to treatment was registered.

Statistical analysis

Variables and outcomes: Continuous variables are presented as arithmetic mean and standard deviations. Qualitative variables are presented as percentage and 95% confidence intervals (95% CI). A level of $p<0.05$ was set as significance cut-off point. *Intention to treat:* includes all randomized eligible patients regardless of the correct follow up or compliance. *Per protocol:* Only patients that have done a correct follow up and a compliance of a minimum of 90% of each study drug.

A multiple logistic regression analysis was performed. The dependent variable was *H. pylori* eradication, and the independent variables were age, sex, reference hospital, smoking habit, diagnosis (ulcer or dyspepsia), adverse events, compliance and treatment. We used a backward modelling strategy, and the log-likelihood ratio was the statistic for model comparison.

Sample size: The hypothesis for the expected efficacy was based in previously published data on sequential and concomitant regimens. Using the formula: $(Z_{0.95} + Z_{0.80})^2$ [Ps(1-Ps) + Pn(1-Pn)} / (Ps-Pn-D)^2 by Blackwelder[23], a sample size of 314 patients was calculated (level of signification alpha = 5%, statistical power = 80%, range of equivalence or hypothesized difference = 10% for a conservative expected response rate of 85% in both regimens). A 10%

maximum lost to follow up has been estimated; therefore the final sample size calculated was 345 patients.

Network Meta-analysis

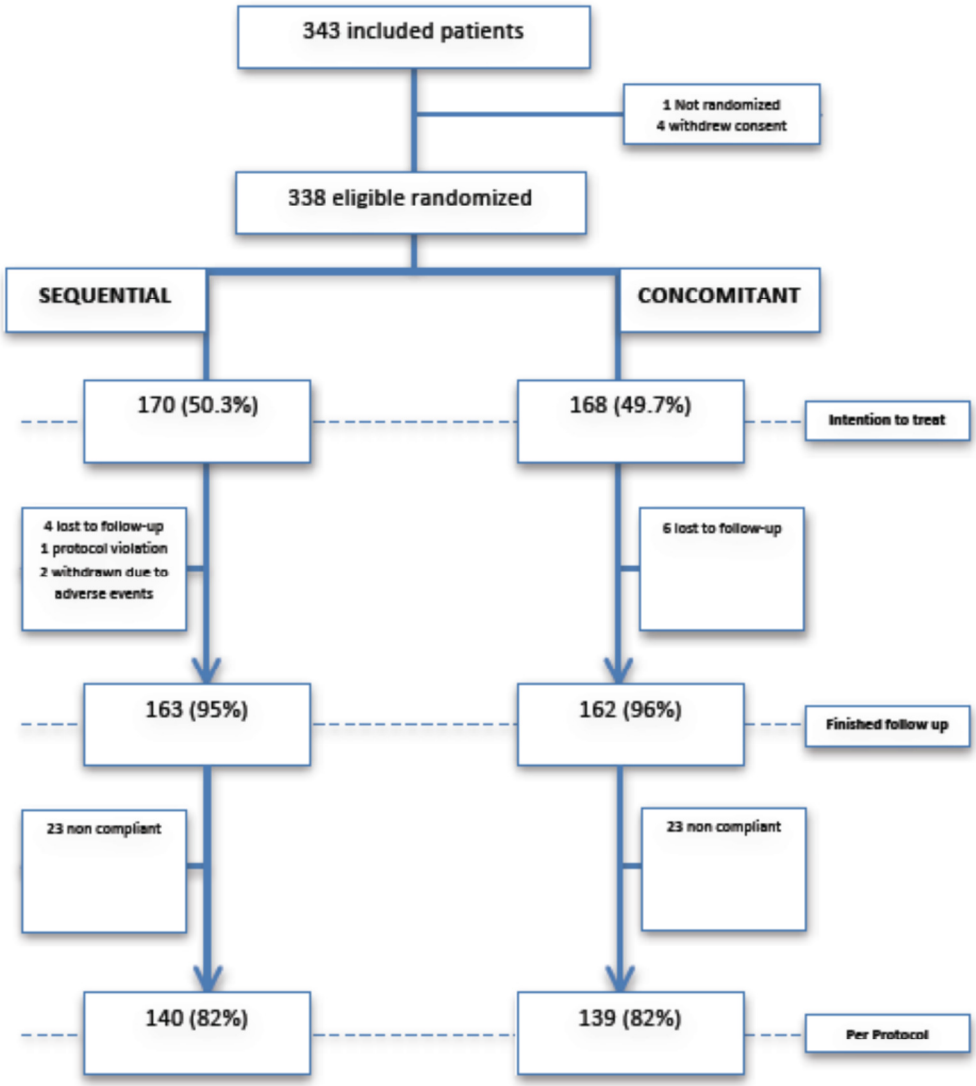
In order to further evaluate the efficacy of sequential and concomitant treatments a network meta-analysis was designed extracting the data from previous direct comparison meta-analyses; sequential versus standard triple therapy, concomitant versus standard triple therapy, and sequential versus concomitant. The extracted data was updated including the recent clinical trials not included in those meta-analyses. *Selection of studies*: Randomized clinical trials comparing concomitant vs. sequential, or comparing them with standard triple therapy. Studies with different treatment arm lengths were excluded. *Search strategy:* bibliographical searches in electronic databases, and manual search of abstracts from Congresses, were conducted up to May 2013. *Data synthesis:* intention-to-treat eradication rate. *Outcome:* Odds Ratio pooled using random effects model. Average efficacy was measured for each treatment multiplying the efficacy in each individual study by its calculated weight.

Using STATA SE 12.0 software the estimated effect of the three different direct comparisons was calculated. For the indirect comparison standard triple therapy was used as common comparator between sequential and concomitant treatments. The pooled effect from both direct and indirect comparisons between sequential and concomitant treatments was compared and combined to obtain a final pooled odds ratio.

RESULTS

A schematic flow diagram of patient inclusion and follow-up process is shown in Figure 1. Of all included patients (343), one was not randomized and four withdrew consent and were erased from the database as required, and therefore were not included in any analysis. The intention to treat population was 338 patients, 170 received sequential treatment and 168 concomitant treatment.

Figure 1. Patient flow diagram



Baseline characteristics of patients are shown in Table 1. There were no significant differences among baseline characteristics among treatment arms regarding any population variable (sex, age, presence of ulcer, smoking habit, nor comorbidities).

Table 1. Baseline characteristics of the studied patients

	Sequential Treatment N = 170	**Concomitant Treatment N = 168**
Women	100 (58.8)	105 (62.5)
Age		
Mean (standard deviation)	47.5 (14.7)	47.3 (15.6)
Median (range)	46 (18-98)	47 (18-86)
Indication		
Dyspepsia		
Functional	71 (41.8)	77 (45.8)
Non-investigated	67 (39.4)	57 (33.9)
Ulcer		
Duodenal	24 (14.1)	24 (14.3)
Gastric	8 (4.7)	10 (6.0)
Smoking Habit	37 (21.8)	38 (22.6)

Data are n (%) unless otherwise indicated.

Efficacy and Compliance

As shown in Table 2, the eradication efficacy of both treatments was equivalent, both in the intention to treat analysis: 86.9% (95% CI = 82-92%) for

concomitant vs. 81.2% (95% CI = 75-87%) for sequential, (p = 0.15); and in the per protocol analysis: 91.2% (95% CI = 86-96%) for concomitant vs. 85.6% (95% CI = 80-91%) for sequential (p = 0.14). No statistically significant differences were found between treatments based on presence or not of ulcer disease, however a trend towards higher eradication rates was found in concomitant regimen for dyspeptic patients compared to those with ulcer disease (88.1% vs. 82.4%, p = 0.1). Compliance for both treatments was also not significantly different: 82.7% (95% CI = 77-88%) for concomitant vs. 82.4% (95% CI = 77-88%) for sequential.

Table 2. Efficacy and compliance

	Sequential Treatment N = 170	**Concomitant treatment N = 168**	**Significance P value**
ITT eradication	138 (81.2)	146 (86.9)	0.15
Dyspepsia	112 (81.2)	118 (88.1)	0.12
Ulcer	26 (81.3)	28 (82.4)	0.91
PP eradication	119 (85.6)	125 (91.2)	0.14
Dyspepsia	96 (86.5)	99 (92.5)	0.15
Ulcer	23 (82.1)	26 (86.7)	0.63
Compliance	140 (82.4)	139 (82.7)	0.93

Data are n (%) unless otherwise indicated. ITT: intention to treat; PP: per protocol

Safety and Adverse Reactions

The list and proportion of adverse reactions is shown in Table 3. Sixty-five percent of the patients referred some kind of discomfort during treatment or

follow-up, whereas adverse reactions appeared in 58.6% (95%CI = 53-64%) of the patients, with an average length of 6.1 days.

Table 3. Adverse Reactions

	Overall N (%)	Sequential N (%)	Concomitant N (%)
Adverse Reactions	**198 (59%)**	**92 (54%)**	**106 (63%)**
Taste distortions	120 (35.9%)	62 (37%)	58 (35%)
Severe	5 (1.5%)	2 (1%)	3 (2%)
Diarrhoea	67 (20.1%)	24 (14%)	43 (26%)
Severe	2 (0.6%)	0 (0%)	2 (1%)
Nausea	36 (10.8%)	17 (10%)	19 (11%)
Severe	3 (0.9%)	0 (0%)	3 (2%)
Abdominal Pain	24 (7.2%)	12 (7%)	12 (7%)
Severe	2 (0.6%)	0 (0%)	2 (1%)
Asthenia	21 (6.3%)	10 (6%)	11 (7%)
Severe	0 (0.0%)	0 (0%)	0 (0%)
Dyspepsia	19 (5.7%)	9 (5%)	10 (6%)
Severe	2 (0.6%)	0 (0%)	2 (1%)
Heartburn	15 (4.5%)	12 (7%)	3 (2%)
Severe	1 (0.3%)	1 (1%)	0 (0%)
Vomiting	14 (4.2%)	5 (3%)	9 (5%)
Severe	3 (0.9%)	0 (0%)	3 (2%)
Anorexia	13 (3.9%)	7 (4%)	6 (4%)
Severe	0 (0.0%)	0 (0%)	0 (0%)

The most common adverse reactions were taste distortions, affecting 120 patients (35.9%, average length 7.1 days), followed by diarrhoea (including any mild increase in number or any softening of stools) in 67 patients (20.1%, average 5.3 days) and nauseas in 36 patients (10.8%, average 5.3 days).

Overall, 59.2% (95% CI = 52-66%) of the adverse reactions were mild and 36.2% were moderate, whereas only 18 (5%, 95% CI = 2-8%) of adverse reactions were of severe intensity (affecting 13 patients, 4%, 95% CI = 1-7%).

The most common adverse reactions not pre-defined in the questionnaire were candidiasis (13 patients), headaches (11 patients), stomatitis (10 patients), other gastrointestinal discomforts (6 patients), skin rash (4 patients), dizziness (4 patients), nervousness-anxiety (4 patients), sleep alterations (4 patients), hepatic biochemical blood test alterations (3 patients) and flu-like symptoms (2 patients). No statistically significant differences were found between treatments in the severity or the rate of adverse reactions: 63.1% (95% CI = 56-70%) with concomitant regimen and 54.1% (95% CI = 47-62%) with sequential treatment (p = 0.09).

Twelve patients discontinued medication due to adverse events, 7 in concomitant treatment vs. 5 in sequential treatment. Although these patients withdrew from treatment, *H. pylori* eradication was still achieved in 6 of them (50%); four (57%) in the concomitant and 2 (40%) in the sequential treatment arms.

Only two serious adverse events were reported, both occurring with concomitant treatment: a vomiting cycle that required emergency room care (lasting 1 day); and a patient that required sick leave from work (10 days) a month after treatment, unrelated to study drugs. However, in both cases patients completed treatment and were not withdrawn from the study.

Multivariate analysis

Multivariate analysis for treatment hospital, sex, age, smoking habit, presence of ulcer, type of treatment and compliance, found association only with compliance (odds ratio of 3.11, 95% CI = 1.73-6.35). However, concomitant treatment showed an odds ratio of 1.54 towards better eradication rate in a borderline significance confidence interval (95% CI = 0.85-2.78).

Network Meta-analysis

Twenty-six trials were included: 13 comparing sequential and standard triple therapies (3,648 patients)[24-36], 8 concomitant and standard triple therapies (1,230 patients)[37-44] and 4 comparing concomitant and sequential therapies (966 patients)[18-20, 45] including the present clinical trial. Data from studies are shown in table 4.

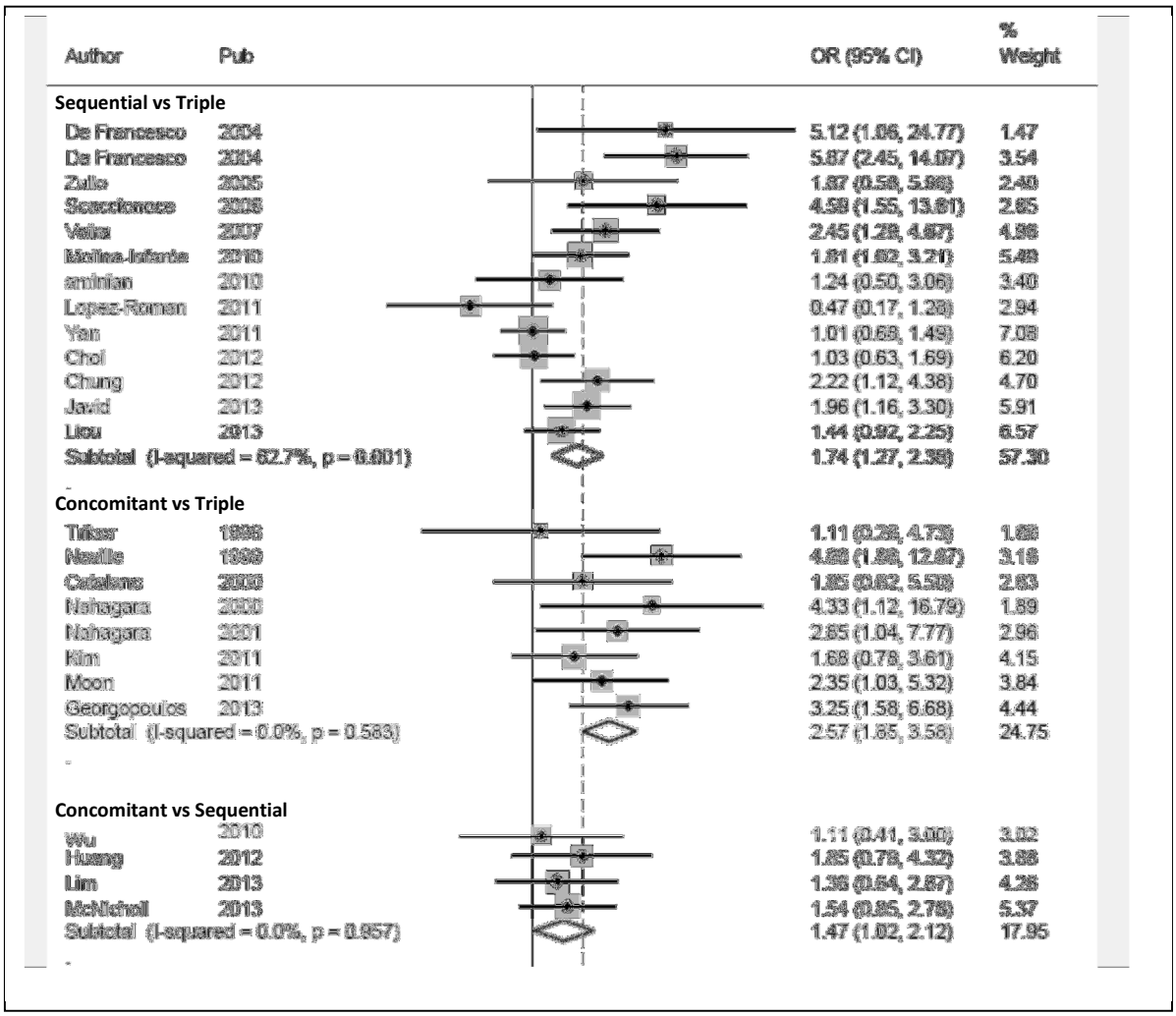
Only the comparison between sequential and standard triple therapies was heterogenous (I^2=62%). Direct comparisons showed significantly lower eradication efficacy of standard triple therapy than sequential (odds ratio = 1.74) and concomitant (odds ratio = 2.57) treatments. Direct meta-analsis comparing concomitant and sequential treatments showed significantly better results for concomitant treatment (odds ratio = 1.47; 95% CI = 1.02-2.12).

Indirect comparison obtained equivalent results: odds ratio = 1.48 95%CI = 0.98-2.36. Network meta-analysis (combining the results from direct and indirect comparisons) demonstrated that concomitant regimen is significantly more efficacious than sequential (odds ratio = 1.47, 95%CI = 1.06-2.05; Number needed to treat = 11) and that results are consistent (data shown on Figure 2).

Table 4. Summary table of Data extraction form

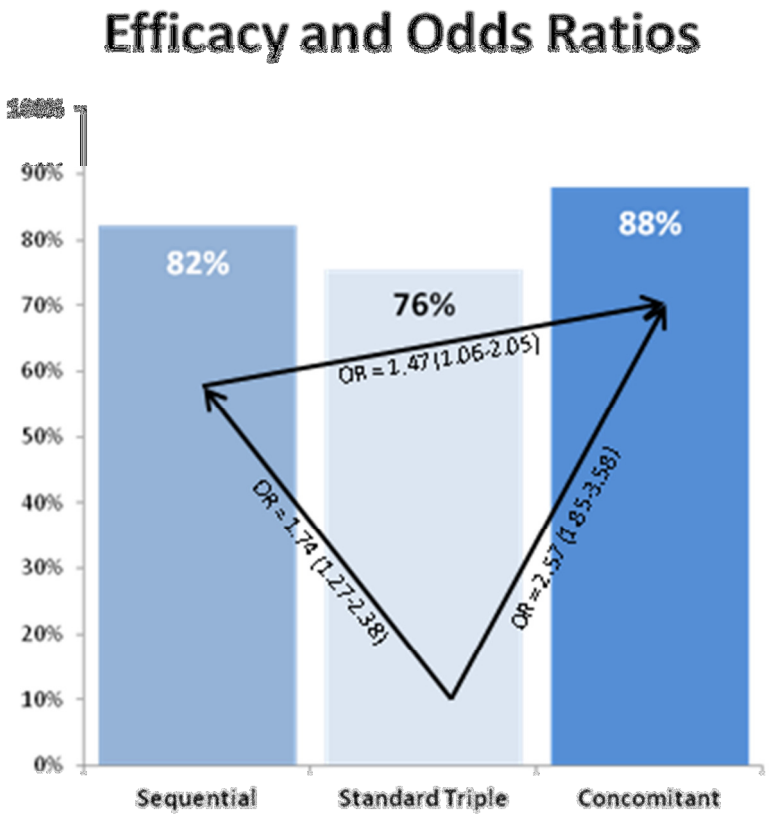
		Standard Triple		Sequential		Concomitant	
Author	**Year**	**Events**	**Total**	**Events**	**Total**	**Events**	**Total**
De Francesco	2004 [34]	42	52	43	45		
De Francesco	2004 [35]	175	231	110	116		
Zullo	2005 [36]	72	80	84	89		
Scaccionoce	2006 [24]	111	141	68	72		
Vaira	2007 [25]	116	150	134	150		
Molina-Infante	2010 [26]	74	115	88	115		
Aminian	2010 [27]	59	90	78	90		
Lopez-Roman	2011 [28]	33	41	27	41		
Yan	2011 [29]	220	293	185	246		
Choi	2012 [30]	259	345	87	115		
Chung	2012 [31]	47	80	60	79		
Javid	2013 [32]	83	134	105	138		
Liou	2013 [33]	247	300	261	300		
Treiber	1998 [37]	38	42			42	46
Neville	1999 [38]	33	56			49	56
Catalano	2000 [39]	45	55			50	56
Nagahara	2000 [40]	40	50			52	55
Nagahara	2001 [41]	65	80			74	80
Kim	2011 [42]	116	135			123	135
Moon	2011 [43]	55	85			43	53
Georgopoulos	2013 [44]	91	123			111	123
Wu	2010 [20]			108	117	107	115
Huang	2012 [19]			68	85	74	84
Lim	2013 [18]			65	86	63	78
McNicholl	2013 [45]			138	170	146	168

Figure 2. Forest plot of network meta-analysis



The calculated weighted pooled efficacy of each therapy was 75.6% with standard triple, 82.1% with sequential and 88.0% with concomitant, equivalent to those obtained in our clinical trial. Overview of weighted pool efficacy and odds ratios network diagram are shown in Figure 3.

Figure 3. Network meta-analysis: Efficacy and Odds Ratios



DISCUSSION

As the efficacy of standard triple therapy does not reach the acceptable threshold of 80% eradication rate in most contexts, new strategies must be sought[11, 46]. In the search of efficacious substitutes of the commonly recommended standard triple therapy, prolonging treatment's duration up to 14 days is an option. However the increase in efficacy is small and it seems unlikely that therapies this long, which may increase side effect rates and reduced compliance, will be generally accepted.

Another alternative is bismuth containing quadruple therapy (PPI, tetracycline, metronidazole and bismuth salts). This treatment is generally recommended as second line treatment after failure with standard triple therapy. Even though it requires taking many pills in a complex scheme, it has demonstrated that it is at least as effective, and as well tolerated, as triple therapies[47]. However, this regimen is not accessible worldwide due to the lack of distribution of tetracycline and bismuth salts in several countries.

The last recommended regimens are the so-called non-bismuth quadruple regimens, which are studied in our trial. Some clinical guidelines include sequential treatment as a first line treatment option[5, 48] and some authors consider it as the best first line option in countries with high resistance rates to clarithromycin[49].

However, the efficacy of sequential treatment seems to be decreasing overtime. A recent meta-analysis[50], promoted by the Cochrane Collaboration, pooling data from all randomized clinical trials comparing sequential vs. standard triple therapy has demonstrated that, although higher efficacy is

achieved with sequential treatment (with and odds ratio of 2.11), the intention to treat effectiveness was not as good as expected (83.5% with sequential vs. 73.8% with standard triple). Moreover, the beneficial effect could not be demonstrated when comparing sequential therapy against 14-day standard triple therapy.

Regarding concomitant therapy, another meta-analysis has shown that non-bismuth concomitant regimens containing a PPI, amoxicillin, clarithromycin and metronidazole achieve almost 90% cure rate, and that its efficacy is significantly better than that of standard triple therapy (odds ratio = 2.36) in randomized trials comparing both regimens[51]. Concomitant therapy has been recommended as first line treatment in the last Spanish Consensus Conference on *H. pylori* infection[52].

The results from our study, mimicking routine clinical practice in Spain, suggest that both sequential and concomitant regimens achieve equivalent, and higher than 80%, *H. pylori* eradication rates in an intention to treat analysis. However, a borderline tendency towards better results with concomitant regimen was found (86% vs. 81%, odds ratio 1.5). Equivalent rates of compliance of approximately 82% were obtained with both regimens, which may explain why both treatments did not achieve higher intention to treat eradication rates. Both treatments showed similarly acceptable safety profiles: approximately 59% of patients presented some discomfort emerged from treatment, although intensity was mostly mild and duration was short. Only two serious adverse events were reported (a vomiting cycle and a sick leave) and were solved without leaving sequels to the patient.

Up to now, 4 studies have compared both non-bismuth treatments head to head for *H.* pylori eradication in a randomized clinical trial and ours is the first one in a European context. Greenberg et al.[21] in a multinational study including nearly 500 patients per arm, compared a 10-day sequential vs. a 5-day concomitant regimens achieving 77% and 74% eradication rates respectively. However, the low efficacy achieved with the concomitant treatment might be explained due to the short regimen prescribed (5 days).

The study by Huang et al.[19] including 85 patients per arm used more similar regimens to the ones prescribed in our study, although they selected lansoprazole instead of omeprazole. The efficacy (sequential = 80% and concomitant = 88%) and the rate of adverse events of approximately 63% reported by their study agree with our results. Huang's study reported a higher compliance, although probably due to the different cut-off point established (less than 70% of drug intake in their study and 90% in ours).

Lim et al.[18] in a pilot Korean study evaluated both regimens lasting 14 days, and achieved 76% intention to treat eradication rates with sequential treatment and 81% with concomitant treatment.

Finally, the Taiwanese study by Wu et al.[20] reported slightly higher *H. pylori* eradication rates with both treatments (approximately 90%). However, the results from the 230 patients included in their study can hardly be compared to our results as they used esomeprazole 40 mg twice daily, which in a recent meta-analysis has demonstrated to improve *H. pylori* eradication efficacy, at least in standard triple therapy[53]. Moreover, the clarithromycin resistance rate was extremely low (6.6%) in comparison with the Spanish (14%) and European rates (17.5%) reported in a very recent multicentre study[10].

The main limitation of our trial is not having evaluated antibiotic resistance in the studied patients; however, the recent publication of the European *H. pylori* resistance to antibiotics study gives a good estimation of the expected resistance (in Spain, 14% against clarithromycin and 28% against metronidazole) in the treated patients[10]. Moreover, the aim of this study was to evaluate sequential and concomitant treatments mimicking routine clinical practice in Spain, where routine antibiotic resistance testing is not usually performed nor recommended[52, 54]. Although acceptable compliance rates were achieved in our study, these figures may be different in clinical practice, especially in primary care. As compliance was the only factor statistically associated with efficacy, prescribing doctors should stress the importance of correct intake to patients, and/or even hand in a treatment diagram for patients to follow and check.

The *H. pylori* eradication efficacy and safety for the sequential and concomitant treatments presented in our study also agree with those reported in the latest observational studies and meta-analyses[16, 51]. Another recent Spanish study has been published[55] in which concomitant and sequential treatments were evaluated. Data from this study shows similar intention to treat results in the untested and antibiotic susceptible patients. For example, concomitant treatment eradication rates for clarithromycin resistant or dual clarithromycin-metronidazole resistance also achieved acceptable results (100% and 75%), although the number of subjects with resistant strains was relatively low.

The performed meta-analysis has been able to update previously published data on the direct comparisons between sequential and standard triple therapy[50], concomitant and standard triple[56] and between concomitant and

sequential[17]. The results from this network analysis have shown statistically significant benefits of using either sequential or concomitant regimens over standard triple therapies, and even a higher efficacy of concomitant treatment over sequential both in direct comparisons and in indirect comparisons.

As using standard triple therapy in clinical trials raises ethical issues, this network meta-analytical approach has allowed comparing the efficacy of sequential and concomitant treatments with the most recommended regimen (standard triple therapy) without using it as a comparator, and therefore not randomizing patients to an already deemed suboptimal treatment arm.

CONCLUSION

In conclusion, given the unacceptable eradication rates of standard triple therapies, the results from our clinical trial suggest that sequential and concomitant regimens offer an acceptable safety profile and compliance rate, and achieve equivalent *H. pylori* eradication rates. Like previous studies, we observed a non statistically significant 5% increase in eradication, allowing to achieve over 90% cure rates with the use of concomitant treatment.

The results from the performed network meta-analysis demonstrate that concomitant treatment offers consistent and significantly better cure rates than sequential treatment in the eradication of *H. pylori*.

Current data suggest that 10-day concomitant regimen for first line treatment may be the most efficient strategy for the eradication of *H. pylori* infection.

CONCLUSIÓN

En conclusión, dadas las tasas de erradicación inaceptables de las terapias triple estándar, los resultados de nuestro ensayo clínico sugieren que los regímenes secuencial y concomitante ofrecen perfiles de seguridad y de cumplimiento aceptables y obtienen tasas de erradicación de *H. pylori* equivalentes. Como ha sido descrito en estudios previos, el uso del tratamiento concomitante mostró un incremento, no estadísticamente significativo, de la tasa de erradicación del 5%, permitiendo obtener más del 90% de eficacia.

Los resultados del meta-análisis en red realizado demuestran que el tratamiento concomitante ofrece de forma consistente y significativa mejores tasas de curación que el tratamiento secuencial en la erradicación de *H. pylori*.

Los datos actuales sugieren que la terapia secuencial de 10 días como tratamiento de primera línea puede ser la estrategia más eficiente para la erradicación de la infección por *H. pylori.*

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CURRICULUM VITAE

DE

ADRIAN GERALD MCNICHOLL

Madrid, junio de 2014

ÍNDICE

1. DATOS PERSONALES

Apellidos y nombre: McNicholl, Adrian Gerald
Fecha de nacimiento: 25 de noviembre de 1980
Especialidad: Biología
Situación profesional actual: Investigador Contratado CIBERehd

2. TITULACIONES ACADÉMICAS

Licenciado en CC. Biológicas por la Facultad de Ciencias de la Universidad Autónoma de Madrid (2005).

Primer año de Doctorado en *Biología Celular y Genética* por la Universidad Autónoma de Madrid (UAM). Mención de Calidad. Cursado con una beca de convenio bilateral en *Tufts University, MA. USA* (2006)

Diploma de Estudios Avanzados por la Universidad Autónoma de Madrid (UAM). "Terapia de Inactivación Fotoquímica in vitro de Helicobacter pylori". Directores: Javier P. Gisbert (Hosp. Universitario de la Princesa) y Trinidad Parra Cid (Hosp. De Guadalajara). Tutor: Jose L. Bella (UAM). Calificación Sobresaliente. (2011)

3. BECAS Y PREMIOS

Beca 2014 Grupo Esófago Estómago Duodeno de la Asociación Española de Gastroenterología, para el proyecto "Rifaximina asociado a la triple terapia clásica (omeprazol, claritromicina y amoxicilina) para la erradicación de *H. pylori*"

IV Beca GETECCU–Otsuka destinada a **proyectos básicos** por el proyecto de investigación: "Implicación del receptor de estrógeno beta (ERβ) en la Enfermedad Inflamatoria Intestinal". 2011.

PREMIO A LA MEJOR COMUNICACION A CONGRESO

Mejores comunicaciones orales

Terapia fotodinámica contra Helicobacter pylori empleando un nuevo material fotosensibilizador. M. Calvino-Fernández, D. García-Fresnadillo, **AG McNicholl**, J.P. Gisbert, T. Parra-Cid. XIV Congreso Nacional de la Asociación Española de Gastroenterología. Madrid, 2011.

4. ACTIVIDAD INVESTIGADORA

4.1. PROYECTOS DE INVESTIGACIÓN COMPETITIVOS. FONDOS PÚBLICOS

TITULO	ENTIDAD	IP	DURACIÓN	PRESUPUESTO CONCEDIDO
Papel del EGF en la regeneración de la mucosa del colon durante la colitis ulcerosa. Implicación del IRS-4	Ministerio de Educación y Ciencia. Plan Nacional de I+D+I (SAF2008-05355)	L. González Guijarro	2008-10	60.000 €
Respuesta T reguladora (CD4+CD25+FOXP3) y patogenia de la infección por H. pylori: relación con el estatus oxidativo de la mucosa gástrica	Fundación para la Investigación Sanitaria de Castilla La Mancha (FISCAM) (Ref. PI-2008/34).	T. Parra	2009-11	64.000 €
Implicación de los factores angiogénicos y linfangiogénicos en la enfermedad inflamatoria intestinal	FIS (REF. PS09/02369)	J.P. Gisbert (Coordinador)	2010-12 (prórroga 2013)	110.715 €
Estudio Fase IV, prospectivo, aleatorizado y comparativo entre la terapia secuencial y concomitante para la erradicación de Helicobacter pylori en la práctica clínica habitual	Ministerio de Sanidad y Política Social (REF. TRA-047)	J.P. Gisbert (Coordinador)	2010-12	61.348 €
Identificación de factores genéticos, ambientales y de expresión fenotípica asociados a la progresión de lesiones precursoras del cáncer gástrico: estudio coordinado español de seguimiento	FIS (REF. PI10/02654)	C. González (J.P. Gisbert: I. Colaborador, Coordinador Gastroenterología)	2011-13	612.210 €
Ensayo clínico multicéntrico, prospectivo, aleatorizado y comparativo para evaluar la eficacia de dos vacunas frente al virus de la Hepatitis B en pacientes con enfermedad inflamatoria intestinal	CAIBER (COMVI-B)	J.P. Gisbert (Coordinador)	2012-14	107.483 €

4.2. PROYECTOS DE INVESTIGACIÓN COMPETITIVOS. FONDOS PRIVADOS

TITULO	ENTIDAD	IP	DURACIÓN	PRESUPUESTO CONCEDIDO
Helicobacter pylori y apoptosis gástrica: influencia de la infección y efecto de la erradicación	Fundación de Investigación Médica Mutua Madrileña	J.P. Gisbert	2007-08	35.000 €

Implicación del receptor de estrógeno beta (ERβ) en la Enfermedad Inflamatoria Intestinal	IV Beca GETECCU–Otsuka	J.P. Gisbert	2011	12.000 €
Estudio prospectivo, aleatorizado y comparativo para evaluar la eficacia de dos vacunas frente al virus de la hepatitis B en pacientes con enfermedad inflamatoria intestinal.	Beca Gonzalo Miño de la Fundación Española de Gastroenterología	J.P. Gisbert	2012	15.000 €

4.3. PROYECTOS DE INVESTIGACIÓN INTERNACIONALES

TITULO	ENTIDAD	IP	DURACIÓN	PRESUPUESTO CONCEDIDO
European Registry on the management of Helicobacter pylori infection	European Helicobacter Study Group	J.P. Gisbert & C. O'Morain	2013-2015	5.800 €
Optimal H. pylori Management in Primary Care	United European Gastroenterology (Long-term Projects)	J.P. Gisbert & L. Agreus	2013-2015	100.000 €

4.4. REDES DE INVESTIGACIÓN

PROYECTO	RED	ENTIDAD	IP	DURACIÓN	PRESUPUESTO CONCEDIDO
Centros de Investigación Biomédica en Red de enfermedades hepáticas y digestivas (CIBERehd)	CIBER	Instituto de Salud "Carlos III"	JP Gisbert	Desde 2008	304.863 €

4.5. ESTUDIOS CLÍNICOS

TÍTULO DEL PROYECTO: A Phase IIIb multicentre, open label induction and double blind comparison of two maintenance schedules clinical trial evaluating clinical benefit and tolerability of certolizumab pegol, a pegylated Fab fragment of humanized antibody to tumor necrosis factor (TNF) over 26 weeks in patients suffering from Crohn's Disease with prior loss of response or intolerance to infliximab
ENTIDAD FINANCIADORA: UCB-Pharma
FECHA INICIO: 2006

TÍTULO DEL PROYECTO: Valor de la calprotectina y lactoferrina fecales en la predicción de la recidiva de la enfermedad inflamatoria intestinal (estudio multicéntrico nacional)
ENTIDAD PATROCINADORA: Grupo para el estudio de la Enfermedad Inflamatoria Intestinal de Madrid
FECHA INICIO: 2006

TÍTULO DEL PROYECTO: Diagnóstico serológico de la gastritis atrófica mediante la determinación de gastrina, pepsinógeno I y II, y anticuerpos frente a H. pylori (Estudio GASTROPANEL) (estudio multicéntrico nacional)
ENTIDAD PATROCINADORA: Asociación Española de Gastroenterología
FECHA INICIO: 2006

TÍTULO DEL PROYECTO: Metotrexato en la Enfermedad Inflamatoria Intestinal (estudio multicéntrico nacional)
ENTIDAD PATROCINADORA: Grupo para el estudio de la Enfermedad Inflamatoria Intestinal de Madrid
FECHA INICIO: 2007

TÍTULO DEL PROYECTO: Mielotoxicidad por azatioprina o mercaptopurina en pacientes con enfermedad inflamatoria intestinal (estudio multicéntrico nacional)
ENTIDAD PATROCINADORA: Grupo para el estudio de la Enfermedad Inflamatoria Intestinal de Madrid
FECHA INICIO: 2007

TÍTULO DEL PROYECTO: Estudio TERA-Hpy: Influencia de los efectos secundarios en la adherencia a la terapia erradicadora de Helicobacter pylori (estudio multicéntrico nacional)

ENTIDAD FINANCIADORA: Teva Pharmaceutical Industries
FECHA INICIO: 2008

TÍTULO DEL PROYECTO: Test de la ureasa "ultrarrápido" para el diagnóstico de la infección por Helicobater pylori (estudio multicéntrico nacional)
ENTIDAD FINANCIADORA: Deltaclon, S.L.
FECHA INICIO: 2008

TÍTULO DEL PROYECTO: Inactivación fotoquímica (fotosensibilización) de H. pylori mediante oxígeno singlete
FECHA INICIO: 2008

TÍTULO DEL PROYECTO: Eficacia y seguridad del tratamiento cuadruple con subcitrato bismuto potasio, metronidazol y tetraciclina administrado durante 10 días con omeprazol para erradicar Helicobacter pylori: en comparación con el omeprazol, amoxicilina y claritromicina administrados durante 7 días (estudio multicéntrico internacional)
ENTIDAD FINANCIADORA: Axcan
FECHA INICIO: 2009

TÍTULO DEL PROYECTO: Open label long term clinical trial evaluating efficacy and safety of chronic therapy with certolizumab pegol, a pegylated FAB fragment of humanized antibody to tumor necrosis factor alpha (TNFalpha) in patients suffering from Crohn´s Disease and having completed C87042 study
ENTIDAD FINANCIADORA: UCB-Pharma
FECHA INICIO: 2009

TÍTULO DEL PROYECTO: Detección de H. pylori mediante RT-PCR e inmunohistoquímica en el paciente con linfoma MALT gástrico H. pylori negativo por métodos convencionales (estudio multicéntrico nacional)
ENTIDAD PATROCINADORA: Asociación Española de Gastroenterología
FECHA INICIO: 2009

TÍTULO DEL PROYECTO: Desarrollo de anticuerpos IgY específicos capaces de reducir el crecimiento de Helicobacter pylori
ENTIDAD FINANCIADORA: AB-Biotics, S.L.
FECHA INICIO: 2009

TÍTULO DEL PROYECTO: Estudio prospectivo para la comparación de la eficacia de dos pautas de vacuna del virus de la hepatitis B en pacientes con enfermedad inflamatoria intestinal
ENTIDAD PATROCINADORA: GETECCU
FECHA INICIO: 2010

TÍTULO DEL PROYECTO: Papel de los receptores de cannabinoides en la enfermedad inflamatoria intestinal
ENTIDAD PATROCINADORA: H.U.Gregorio Marañón
FECHA INICIO: 2011

TÍTULO DEL PROYECTO: Eficacia y seguridad de PYLERA (subcitrato potásico de bismuto, metronidazol y clorhidrato de tetraciclina) con omeprazol, administrados 10 días en sujetoso con fracaso del tratamiento de erradicación de Helicobacter pylori.
ENTIDAD PATROCINADORA: Aptalis.
FECHA INICIO: 2012.

TÍTULO DEL PROYECTO: Estudio clínico para evaluar el efecto de un complemento alimenticio en el alivio de síntomas de antibioterapia en pacientes tratados para la infección por Helicobacter pylori
ENTIDAD PATROCINADORA: Casen-Fleet.
FECHA INICIO: 2013.

5. PUBLICACIONES

5.1. REVISTAS INDEXADAS

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6. **OTROS MÉRITOS**

Coordinador de los siguientes proyectos y actividades científicas:

OptiCare *(Optimal* H. pylori *management in Primary Care). Proyecto educativo a largo plazo para la formación continuada en medicina de Familia y Comunitaria. Coordinador Internacional*

Hp-EuReg *(European Registry on the Management of* H. pylori*). Coordinador Comité Científico Internacional*

Secretario científico de la *III Conferencia de Consenso Española sobre "Tratamiento de la infección por Helicobacter pylori".* (2012).

Secretario Científico de la *I Conferencia de Consenso Española sobre la Colitis Microscópica.* (2014)

Miembro de la Asociación Española de Gastroenterología

Coordinador Comité Local del XXVIth International Workshop on Helicobacter and related bacteria in chronic digestive inflammation and gastric cancer. Madrid 2013.

Coordinador de las líneas de *H. pylori* del grupo CIBER (Centros de Investigación Biomédica en Red) de Enfermedades Hepáticas y Digestivas (**CIBERehd**) del Dr. Gisbert en el Hospital Universitario de La Princesa. Clasificado en la categoría de EXCELENTE, atendiendo a los criterios de producción científica, capacidad de transferencia, conectividad y alineación con los descriptores del CIBERehd.

Vocal de la **Unidad de Innovación** del **Instituto de Investigación Sanitaria** Hospital Universitario de La Princesa, encargada del análisis de las nuevas tendencias **tecnológicas y de su implementación en el Instituto.**

Coordinador de *H. pylori* en el Grupo de la Línea de Investigación "Enfermedades inflamatorias esófago-gastro-intestinales" del Instituto de Investigación Sanitaria Hospital Universitario de La Princesa.

Colaboración Cochrane:

*OP Nyssen, **AG McNicholl**, F Megraud, V Savarino, G Oderda, C Fallone, L Fischbach, F Bazzoli,* JP Gisbert*. Sequential versus standard triple therapy for Helicobacter pylori eradication (Cochrane Protocol).*

Revisor de manuscritos de Gastroenterología de las siguientes revistas nacionales e internacionales:

Gastroenterology
Gut
American Journal of Gastroenterology
Alimentary Pharmacology and Therapeutics
Helicobacter
Gastroenterología y Hepatología